Remarks

Applicants appreciate the thorough examination of the present application as evidenced by the final Office Action dated November 28, 2007 (hereinafter, the "Final Action"). Claims 16, 22, 31-33, 42 and 44-47 are pending upon entry of the present Amendment. Claims 16, 22, 31-33, 42, 44 and 47 are rejected. Claims 45 and 46 are objected to in the Final Action. Applicants respectfully submit that no new matter is introduced by the claim amendments presented herein, as will be discussed in detail below, and Applicants respectfully request entry of these amendments.

Applicants also respectfully submit that the pending claims are patentable over the cited references at least in view of the reasons previously made of record, the amendments presented herein and the presently submitted remarks.

More specifically, regarding the rejection of Claims 16, 22, 33, 42 and 47 under 35 U.S.C. §103(a), Applicants respectfully submit, in contrast to the assertions of the Final Action as well as previous Office Actions, that one of ordinary skill in the art would not be motivated to modify the teachings of Silvestris et al. or Bukowski et al. to arrive at the present invention recited in Claims 16, 22, 33, 42 and 47 or found it obvious to try the methods of these claims. At a minimum, as previously noted, it was not routine practice at the time of filing the present application to provide erythropoietin (EPO) in the manner suggested by the Examiner to render the present invention obvious at least because those skilled in the art were apprised of the potential detrimental effects of providing EPO prophylactically as suggested by the Examiner. The risk of detrimental effects of death, thrombosis and stroke that can be associated with attempting to increase hematocrit levels in patients who do not suffer from anemia far outweighed any perceived potential benefit of preventing anemia. Thus, the methods proposed in the pending claims are not obvious in view of the cited references and/or in view of the knowledge possessed by one of ordinary skill in the art.

Applicants further submit that Claims 31, 32 and 44 comply with the written description requirement. Applicants have amended these claims to recite the endothelial protecting amount described in the application, i.e., 100 Units per kilogram to about 200 Units per kilogram. Applicants further note that EPO is a hormone that is primarily produced in the kidneys and secreted into the blood. Therefore, EPO is in direct contact with the

endothelium. The blood of each individual is approximately 5% of the total body weight. For example, an individual of 70 kg has approximately 3.5 kg or 3.5 liters (3500 mL) of blood. Thus, 50 mL of blood corresponds to approximately one kilogram of body weight. Therefore, the range of 100-200 Units per kg corresponds to approximately 2-4 Units per mL of blood.

However, as understood by those skilled in the art, the effective amounts of a test substance *in vivo* (preclinical models and humans) are frequently higher than those used *in vitro*. Thus, in order to see an effect in whole organisms, it is routine practice in many laboratories (including the inventors) to use at least 10 times as much test substance in *in vivo* models as that used *in vitro*. Therefore, after taking into consideration the *in vivo* factor of 10, 2-4 Units of EPO per mL *in vivo* would correspond to 0.2-0.4 Units of EPO per mL *in vitro*.

Applicants further submit that Claims 16 and 33 are not anticipated by Silvestris et al. at least where Silvestris et al. fails to provide an enabling disclosure for methods of treatment as recited in these claims for at least the reasons previously made of record, and at a minimum, where the cited reference fails to teach the invention and EPO does not inherently reduce endothelial injury as recited in Claims 16 and 33.

Lastly, Claims 45 and 46 have been amended to address the claim objections. Accordingly, Applicants submit that rejections and objection to the claims have been overcome.

Conclusion

Applicants respectfully request that all outstanding rejections to the claims be withdrawn and that a Notice of Allowance be issued in due course. In any event, any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

Respectfully submitted,

F. Michael Sajovec
Registration No. 31,793

USPTO Customer No. 20792
Myers Bigel Sibley & Sajovec, P.A.
P. O. Box 37428
Raleigh, North Carolina 27627
Telephone: (919) 854-1400
Facsimile: (919) 854-1401

CERTIFICATION OF TRANSMISSION

I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) to the U.S. Patent and Trademark Office on April 28, 2008.

Betty Lou Rosser
Date of Signature: April 28, 2008